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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,696	10/31/2001	Donald Davies	2190/49927	8654

23911 7590 08/23/2004

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EXAMINER	
MARVICH, MARIA	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,696	DAVIES, DONALD	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-82,84 and 85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-82 and 84-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 5/25/04. Claims 1-40 and 83 have been canceled. Claims 41, 44, 46-48, 61, 63, 64, 66, 68-70, 72, 75-80 and 85 have been amended. Claims 41-82 and 84-85 are pending.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are new grounds of rejection herein that were necessitated by applicant's amendment and therefore, this action is final.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 45-46, 53-55, 57-58, 60-82 and 84-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 45 is unclear for reciting "viral based vector". A viral based vector is not defined by the specification or the prior art. It is unclear how much of the vector must be viral to be viral based or do specific viral components make the vector "viral-based". If specific viral components makeup the "viral-based vector", what components are required? **This rejection is maintained for reasons of record in the office action mailed 2/25/04.**

Claim 45 recites "said viral based vector" in claim 44. There is no antecedent basis for this limitation in the claim. **This is a new rejection necessitated by applicants' amendment.**

Claim 46 is vague and indefinite in that the metes and bounds of the term "derived from" are unclear. It is unclear the nature and number of steps required to obtained a "derivative" of a virus. The term implies a number of different steps that may or may not result in a change in the functional characteristics of the vector from the source that it is "derived from". It would be remedial to amend the claim language to use the term "obtained from", which implies a more direct method of acquiring the vector. **This is a new rejection necessitated by applicants' amendment.**

Claims 53-55 and 57-58 recites "said gene encoding a polypeptide having p450 activity" in claims 41, 53-54 and 57. There is no antecedent basis for this limitation in the claim. **This is a new rejection necessitated by applicants' amendment.**

Claim 60 is vague and indefinite in that the metes and bounds of "a gene or part thereof encoding a polypeptide having p450 activity" are unclear. The specification does not define "p450" activity and therefore it is not clear what criteria exist for identifying the polypeptides to be included in the invention or which biological activity is referred to by the term "p450 activity". **This rejection is maintained for reasons of record in the office action mailed 2/25/04.**

Claim 63 is vague and indefinite in that the metes and bounds of "expression of the polypeptide is controlled by a promoter sequence" are unclear. A promoter controls the expression of a polynucleotide not a polypeptide. **This is a new rejection necessitated by applicants' amendment.**

Claim 64 is vague and indefinite in that the metes and bounds of "substantially: are unclear. The term "substantially" is a relative one not defined by the claim, no single set of

condition is recognized by the art as "substantial" and because the specification does not provide a standard for ascertaining the requisite degree, the metes and bounds of the claim are unknown. **This rejection is maintained for reasons of record in the office action mailed 2/25/04.**

Response to Amendment-35 USC 112, second paragraph

Applicants traverse the claim rejections under 35 U.S.C. 112, second paragraph on pages 10-11 of the amendment filed 5/25/04. Applicants argue that relevant claims have been amended to overcome claims rejected for indefiniteness. Additionally, applicants traverse the rejection of "substantially" in claims 64 and 67-68. Applicants argue that a promoter that directs expression predominantly in a tissue or development stage, this promoter is specific for that tissue or stage. In the context of the instant invention, applicants argue that the term "substantially" is permissible and its meaning is clear (see MPEP 2173.05(b)(D).

Applicants' arguments filed 5/25/04 have been fully considered but they are not persuasive. While applicants have indicated that all claims have been amended to overcome the claim rejections, it appears that some claims were inadvertently overlooked. For example, claims 44-46, 66 and 68 were rejected for reciting viral based vector. In the amendment filed 5/25/04, claims 44, 46, 66 and 68 have been amended by deletion of "based". However claim 44 still recites viral based vector. The remaining claims that have not been amended to overcome the rejections in the office action mailed 2/25/04 are described above. The MPEP has noted that in certain instances, use of the term "substantially" is definite. Specifically, for example "substantially" can be definite in view of general guidelines contained in the specification or when used with "substantially equal". In the instant case, the specification does not provide

general guidelines for the measure of "substantially tumor cell specific expression. The use of substantially in the instantly recited claims is not similar to its use to describe equal as equal is a measurable term which defines the term "substantially". As used in the instant claims the term "substantially" is a relative one not defined by the claim, no single set of conditions is recognized by the art as being "substantial".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-54, 59-76, 79, 81-82 and 84-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment.**

The limitation "polypeptide having a p450 activity of converting acetaminophen to a cytotoxic molecule" has been added to claim. Applicant has not indicated where support for this limitation is found. The examiner has been unable to find literal support in the originally filed specification for the term "polypeptide having a p450 activity of converting acetaminophen to a cytotoxic molecule". The specification teaches that CYP1A2, CYP2E1 and CYP3A4 encode polypeptides that convert acetaminophen to NABQI which is a cytotoxic molecule. Therefore,

the limitation of "polypeptide having a p450 activity of converting acetaminophen to a cytotoxic molecule" is impermissible NEW MATTER.

Claims 41-82 and 84-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 53-58 and 60-62 read on a genus of vectors comprising genes (or effective part thereof) encoding a polypeptide having p450 activity. **This rejection is maintained for reasons of record in the office action mailed 2/25/04.**

Claims 41-55, 57-77, 79-82 and 84-85 recite a broad genus of polynucleotides that encode a polypeptide having a p450 activity of converting acetaminophen to a cytotoxic molecule. **This is a new rejection necessitated by applicants' amendment.**

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

In the instant case, applicants do not disclose any of the claimed genes. The specification discloses that "CYP1A2, also to a much lesser extent CYP2E1 and CYP3A4" are genes that encode a polypeptide having p450 activity (page 3, line 5-9). The **cDNA** of CYP1A2 is used for

cloning and expression purposes. The genes are completely unknown at the onset as the invention and the genes encoding polypeptides that have p450 activity are not disclosed. The genomic version of any of the recited genes is not disclosed by the specification nor does the prior art apparently disclose the entire gene. While the cDNA may be known, not all of the genes have been characterized. Because all of the components of the gene such as regulation sequences, introns, and exons must be determined empirically in order to generate the p450 genes, applicant claims the gene without sufficient disclosure about its structure. The skilled artisan would not conclude that applicant was in possession of viral vector comprising the claimed genes.

In the instant case, applicants recite use of a polynucleotide encoding a polypeptide having p450 activity of converting acetaminophen to a cytotoxic molecule. Applicants have not disclosed this broad genus of polynucleotides. The disclosure teaches that CYP1A2 and to a lesser extent CYP2E1 and Cyp3A4 are genes expressed by the liver and this enzyme converts acetaminophen to N-acetylbenzoquinoneimine (NABQI). CYP1A2 has been cloned and is used to demonstrate *in vitro* cell killing in the presence of acetaminophen. Applicants do not disclose the sequences of the any of the genes or polynucleotide sequences that encode a polypeptide having p450 activity. It is not clear that if disclosed polynucleotides other than CYP1A2 would encode polypeptides having p450 activity of converting acetaminophen to NABQI. The specification fails to reduce to practice or provide clear depiction of properties or structures of polynucleotides encoding polypeptides that have p450 activity and that convert acetaminophen to NABQI. Therefore, as the specification fails to describe the requirements of the polynucleotide such that a structure-function nexus is readily apparent to the skilled artisan, the

relevant identifying characteristics are unknown. In an unpredictable art, the disclosure of one species would represent to the skilled artisan a lack of a representative number of species sufficient to show applicants were in possession of claimed genus. Given the diversity of polynucleotides and the lack of written disclosure of the structural characteristics, it is concluded that applicant was not in possession of their invention.

Response to Amendment-35 USC 112, first paragraph

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph for lack of written description on pages 11-12 of the amendment filed 5/25/04. Applicants argue that relevant claims have been amended to overcome claims rejected for lack of rejection by replacing "gene or part thereof" with " a polynucleotide" and by specifying the activity of the encoded polypeptide.

Applicants' arguments filed 5/25/04 have been fully considered but they are not persuasive. While applicants have indicated that all claims have been amended to overcome the claim rejections, it appears that claims 53-58 and 60-62 were inadvertently overlooked. However, the amendments to the claims that recite that the activity of p450 is limited to "converting acetaminophen to NABQI" do not meet the guidelines for Written Description which state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art". In the instant case, while the functional requirements of the polynucleotide are disclosed, the structure of the recited polynucleotides is not such that the structural functional requirements of the recited construct can be envisioned.

Claims 41-82 and 84-85 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record in the office action mailed 2/25/04.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites a composition comprised of acetaminophen and a vector encoding p450 and methods of using these compositions to treat cancer. The invention utilizes disciplines of molecular biology, virology and clinical technology.

2) **Scope of the invention**. The vector comprises a gene encoding a polypeptide having p450 activity, which converts acetaminophen into a metabolite called N-acetylbenzoquinoneimine (NABQI). Exposure of cancer cells to this metabolite leads to cytotoxicity. The invention recites use of this vector in conjunction with doses of acetaminophen that are lethal to cancer cells but not to normal liver cells. The method is directed toward gene therapy in mammals and humans using gene delivery protocols such as viral vector delivery.

The only disclosed utility for practicing the claimed methods is for gene therapy. These steps of gene therapy exacerbate an already complex method.

3) **Number of working examples and guidance**. It is stated that administration of acetaminophen at high doses leads to levels of NABQI sufficient to kill cancer cells while normal liver cells are not killed. Purportedly, this is due to a difference in glutathione level in the cancer cells versus the liver cells (page 4, line 8-12). To further protect normal liver cells, it is suggested that a non-human p450 gene can be used in the invention in the presence of furaphylline, which inhibits function of human CYP1A2 (page 4, line 26-31). Methods are provided to increase the intracellular concentration of liver glutathione to detoxify NABQI and by the administration of methionine and acetylcysteine. Applicants state that it might be possible to increase the efficiency of the system by replacing CYP1A2 with human CYP2E1 and CYP3A4 and rodent forms of these enzymes. However, other than human CYP1A2, the enzymes have not been analyzed.

Applicants assay the effects of p450 in the presence of acetaminophen using *in vitro* cell systems. The guidance for delivery of the vector to a mammalian subject is broad and general i.e. administration includes but is not limited to intravenous, intramuscular, intraperitoneal injection or direct injection into the tumour tissue (page 10, line 21-24). The instant specification fails to demonstrate any examples or specific guidance for introduction of the composition comprising a vector encoding a polypeptide having p450 activity and acetaminophen into a mammalian subject. There are no disclosures for *in vivo* concentration of vector or acetaminophen, no dose schedules and no determination of subjects for which the method would be directed. The instant examples are directed to methods of establishing stable

and transient cell lines expressing p450. Experiments with transfected COS and H1A2 MZ cell lines demonstrate that *in vitro* acetaminophen in the presence of CYP1A2, leads to cell death. Variable bystander effects were identified in several cell lines incubated with stably expressing H1A2 MZ cells.

4) **State of Art**. The art of gene therapy for the treatment of cancer is a high art. Enormous efforts have been directed toward the development of gene therapy vectors and for cancer treatments. Each goal alone is complex and requires great skill in the art.

5) **Unpredictability of the art**. In general, many parameters must be addressed for *in vivo* gene delivery such as lack of toxicity to normal tissues, and the effect of the immune response as well as doses to be administered, dose schedules etc. The instant invention addresses the issue of cytotoxicity of cancer treatment to normal tissue. However, given the lack of *in vivo* experimentation, the data cannot be assessed. While *in vitro* models have been provided as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the *in vitro* transfection systems and the human disease state.

The unpredictable nature of gene therapy is exacerbated due to the lack of recited methods and because the genes are completely unknown at the onset as the invention. For example, while applicants disclose that cDNA encoding CYP1A2 can be used in the *in vitro* experimental system, the genes encoding polypeptides that have p450 activity are not disclosed. It is not clear that even if the genes were disclosed that the polypeptides encoded by the genes

would function in a manner commensurate with that of the disclosed vector comprised of cDNA from CYP1A2. The route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma et al. (Verma et al. Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression". To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols. The invention specifically recites use of viral vector s for delivery, use of viral vectors in gene therapy is highly unpredictable in the art. Meng and Deiry (Gene Therapy of Cancer, 1999, page 6, column 1) teach that means of delivery other than intratumoral injection compound the obstacles associated with adenoviral use. "Tropism for organs such as liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous of the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass". "While reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle positioned in a tumour deposit. This strategy achieves a relatively low efficiency of gene delivery, which is confined to tumour cells immediately adjacent to the needle track. Plasmids or viral particles delivered in this way do not permeate freely through the interstitial fluid bathing the tumour." (Russell, p 1165, column 2). The level of infection necessary to achieve therapeutic affects of the heterologous gene without toxicity to normal cells that results from leaky expression of the viral genes required for replication is unknown. As noted by Marshall, (Marshall et al., Science January 17, 2003) one of the main issues in using retroviral vectors for gene therapy is determining how to use the vector in vivo without causing leukemia or other

cancers in the patients being treated. This is not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled artisan can make and **use** the claimed invention for the recited treatments. No viral vector has proven adequate sources of gene delivery vehicles to date.

6) **Summary**. The invention recites a complex series of methods for the treatment of cancer using a vector encoding p450 and acetaminophen. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols and the inability to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Amendment-35 USC 112, first paragraph

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph for lack of enablement on pages 12-16 of the amendment filed 5/25/04. Applicants argue that the invention has been rejected for lack of patentable or credible utility. Applicants traverse this rejection for the following reasons. First, the courts have found that the mere identification of a

pharmacological activity of a compound that is relevant to an asserted pharmacological use satisfies the utility requirement. Secondly, utility for therapeutic inventions is held despite the early stage of the development of the pharmaceuticals as *in vitro* testing may establish a practical utility. Thirdly, therapeutic utility is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs. Fourth, applicants state that the discussion of all the potential side effects of some of the viral vectors in gene therapy in the Office action is irrelevant for the legal analysis of enablement. As evidence, applicants describe successful examples of gene therapy.

Applicants' arguments filed 5/25/04 have been fully considered but they are not persuasive. The requirement of 35 U.S.C. 112, first paragraph as to how to use the invention is different from the utility requirement of 35 U.S.C. 101. According to the MPEP, "If an applicant has disclosed a specific and substantial utility for an invention and provided a credible basis supporting that utility, that fact alone does not provide a basis for concluding that the claims comply with all the requirements of 35 U.S.C. 112, first paragraph. For example, if an applicant has claimed a process of treating a certain disease condition with a certain compound and provided a credible basis for asserting that the compound is useful in that regard, but to actually practice the invention as claimed a person skilled in the relevant art would have to engage in an undue amount of experimentation, the claim may be defective under 35 U.S.C. 112, but not 35 U.S.C. 101." (see MPEP 2164.07). The instantly recited claims have not been rejected based upon a lack of utility but for lack of enablement. Specifically, the instant claims have been rejected for lacking adequate teachings for use of the instantly recited method steps for *in vivo* gene therapy. The invention as disclosed does not provide the skilled artisan with the ability to

use the compositions and methods to treat a patient with cancer. No *in vivo* protocol steps or teachings have been provided. Essential factors not taught include treatment intensity, accompanying immune-suppression drugs and schedule treatments as well as amount of viral vectors to be used. Applicants' recite that viral vectors can be used to deliver the nucleic acids into the cells. As stated above, no viral vector has proven adequate sources of gene delivery vehicles to date. And use of viral vectors is "not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled artisan can make and **use** the claimed invention for the recited treatments". Finally, any prophetic recitations of success in gene therapy cannot be extrapolated back to the instant invention as it is not clear that the specification has support for the teachings of said references. Therefore, neither the specification nor the prior art teach one how to **use** the instantly claimed invention.

Conclusion

No claims are allowed.

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER